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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/647,561 | 08/25/2003 | Michael David Bentley | 034848/268660 | 3230 |

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| EXAMINER | |
|---|---|
| HEARD, THOMAS SWEENEY | |
| ART UNIT | PAPER NUMBER |
| 1654 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 02/05/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/647,561 | BENTLEY ET AL. | |
| | Examiner | Art Unit | |
| | Thomas S. Heard | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/21/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,6-19,21,23,24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-19,21,23,24,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The Applicants Amendments to the claims received on 11/21/2006 is acknowledged. Rejections or objections not addressed in this office action with respect to the previous office action mailed 8/8/2006 are hereby withdrawn.

Claims 1-3, 6-19, 21, 23, 24, 26, and 27 are currently pending.

### *Claim Rejections - 35 USC § 112*

Applicant's arguments, see page 5, filed 11/21/2006, with respect to 112 2nd paragraph rejection have been fully considered and are persuasive, as the claim has been cancelled. The rejection of claim 5 has been withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's arguments, see page 5, filed 11/21/2006, with respect to the rejection(s) of claim(s) 5 under 112 2nd paragraph have been fully considered and are persuasive, as Applicants have cancelled the claim. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of incorporating the language that resulted in the previous rejection into claim 1.

Claims 1-3, 6-19, 21, 23, 24, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 1, the phrase "...wherein said conjugate is absent non-covalent bonds" remains indefinite as to what is being claimed. The Examiner is well aware of what a non-covalent bond is, but in light of the claim is it still unclear. For example, is the Applicant's invention devoid of any ionizable sidechains or C-terminal carboxylate or amidate? These would be readable on the non-covalent bonds in the conjugate.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-19, 21, 23, 26, and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304 and Wu D, Pardridge WM., "Neuroprotection with noninvasive neurotrophin delivery to the brain," Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):254-9.

Applicant's arguments filed 11/21/2006 have been fully considered but they are not persuasive. Applicant have argued that Delgado does not suggest a biphalin or a

DPDPE PEG conjugate that is capable of transporting a compound across the BBB. The Examiner agrees, as with a 103 rejection, at least two references are usually required to make a prima facia obviousness case. The Delgado reference was used to provide a number of motivating reasons that one would want to pegylate their protein, such as increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility, among other properties of the PEG-protein conjugates. Thus, the reason one may be motivated to pegylate a protein may be different. However, the reason Wu used the PEG was to reduce rapid uptake by the peripheral tissue which is readable and in agreement with Delgado motivation of increased plasma half-life.

Applicant have further argued that the PEG is conjugated to biotin (non-covalent) and is a three component conjugate whose BBB transport is facilitated by OX26 Mab and not PEG. This is also unpersuasive as the claim is directed to a peptide comprising a peptide, thereby reading on more than a two-component system. Further, the PEG is covalently attached to the neurotrophic factor (BDNF) and not via biotin, see Applicants own illustration on page 7 and that in the cited reference by Wu.

Given that the claims are drawn to a peptide comprising, the additional components of biotin, and OX26 Mab are still readable on the instantly claimed invention. The neurotrophic BDNF was pegylated in the reference by Wu, and this pegylation is well within the reasons and motivation to pegylate any pharmaceutically

acceptable peptide for reason provided by Delgado. There are a plurality of reasons to Pegylate a protein.

As stated in the previous Office action mailed 8/8/2006, Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al teaches the generic benefits of PEGylating a protein which are increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility, among other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000 MW readable upon n ranging from 10 to 2000 for $-CH_2CH_2O-(CH_2CH_2O)_n-CH_2CH_2-$ in claim 27. See entire Review Article. Delgado et al does not teach the pegylation of the neuropeptide biphalin.

Wu et al teaches a neuropeptide (BDNF) that has been PEGylated (2000 MW) and further chemically modified to include a biotin/OX26Mab composition (diagnostic agent by the Applicant's specification) on the terminus of the PEG for transport across the blood brain barrier (BBB). Thus, the neuropeptide (BDNF) had the benefits of PEGylation taught by Delgado et al with the added capacity to transport across the BBB. Wu et al states that "there are more than 30 known neurotropic factors and there molecules may prove to be powerful neuropharmaceuticals should they be enabled to undergo transport through the BBB with optimized plasma pharmacokinetic properties.

The results of the present investigation indicate that if the neurotrophic factor undergoes a defined molecular reformulation, such as that depicted in Fig. 1, both to enable BBB transport [biotin/OX26Mab] the addition of and to optimize plasma pharmacokinetics [Pegylation], then these molecules may have therapeutic effects in the brain after peripheral administration," see full article.

It would have been obvious at the time of the instantly claimed invention to PEGylate biphalin for the benefits of increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility among other as taught by Delgado et al. One would have been motivated to do so given that the benefits of PEGylation are not protein specific as also demonstrated by Delgado et al. One would have had a reasonable expectation of success given that many unrelated proteins have been PEGylated and shown to have these benefits and that PEGylation is a well-known and common modification in the peptide/protein arts. One would have been also further motivated with reasonable expectation of success to modify the PEG moiety to extend BBB transport as taught by Wu et al given Wu's clear teaching that this is extendable to many other neuropeptides with only the need for optimization. Therefore, it would have been prima facia obvious to one of ordinary skill in the art at the time of the instantly claimed invention to PEGylate and conjugate the PEG to OX26/Strepavidin for improved pharmacokinetics and BBB transport.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Inada, et al, "Modification of Proteins with Polyethylene Glycol Derivatives," Methods in Enzymology, (1994), Vol 242, 65-90.

## Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TSH

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